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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/425,742	10/22/1999	KARL THEODOR KRAEMER	DEAV1998/L071 US NP	9957

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EXAMINER	
YU, GINA C	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/425,742	KRAEMER ET AL.	
	Examiner	Art Unit	
	Gina C. Yu	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,28,29 and 39-44* is/are pending in the application.

4a) Of the above claim(s) *3,9 and 41-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10-23,28,29,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of response filed on April 13, 2007. Claims 1-23, 28, 29, and 39-44 are pending, of which claims 3, 9, 41-44 are withdrawn from consideration. All rejections made under 35 U.S.C. § 103 (a) as being unpatentable, as indicated in the previous Office action dated March 27, 2006, are maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4, 7, 8, 11-13, 16, 17, 22, 23, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, III et al. (US 4946870) in view of Encyclopedia of Controlled Drug Delivery, (Vol. 1 & 2, 1999) and Gaillard-Kelly et al. (US 5411981).

Partain teaches a topical film-forming composition for delivering pharmaceutical actives with controlled release. The reference teaches that the composition is useful as a delivery system for single or combination of pharmaceutical active agents, including antiacne agents (retinoic acid and benzoyl peroxide) and anti-alopecia agents (Minoxidil). See col. 9, lines 15 –16; Examples 1, 15, and 18. See instant claims 22, 23, 28, and 29. The reference also teaches using pharmaceutical actives including diazoxide and nifedipine, diltiazem are taught in col. 8, lines 55 – 58. See instant claims 11 and 12. The reference teaches that chitosan derivatives are useful film formers and topically applied in the form of lotion, solution, cream, etc. See col. 3, lines 28 – 52. The

polymer is said to readily form a film and "acts as a reservoir to continuously deliver the actives as well as protect the tissue from further injury or insult", which negates the need of hair cover. The reference goes on to teach that the film gives uniform distribution of the active on the tissue and prevents the migration or loss of the active from the site of application, and helps to control the dosage at a constant level. The reference also teaches using solvents including ethanol and glycerine with the chitosan film-forming agent. See col. 9, line 58 –66; col. 10, lines 10-17; Example 14.

Partain does not specifically mention that a plasticizer is used in the composition, but glycerine, as used in Example 14, is a well-known plasticizer in controlled release pharmaceutical art. See Encyclopedia of Controlled Drug Delivery, p. p. 307, Table 1; p. 309.

Partain fails to teach the compound of instant formula I.

Gaillard-Kelly et al. teach that the phenylimidazolidines of instant formula I have anti-androgenic activity and are used in pharmaceutical compositions including creams, pomades, and lotions. See col. 9, lines 29 – 36. The reference teaches that the compositions useful for treatment of acne and androgenic alopecia, among others. See col. 9, lines 43 – 55. The reference specifically teaches that the compositions are "useful in dermatology" and can be used antiacne components such as retinol or with a product stimulating the growth of hair such as Minoxidil (6-amino-4-4-piperidino-1, 2-dihydro-1-hydroxy-2-iminopyridimidine) for the treatment of alopecia. See col. 9, lines 56 – 65. See instant claims 11, 13, and 23. Example 96 teaches 4-[3-(4-hydroxybutyl)-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile. See instant

claim 4. The reference also teaches adding to the composition 5 alpha-reductase inhibitor, which meets instant claims 16 and 17. See col. 9, lines 56 – 61. The reference also teaches that glycols are suitable excipients for the compound. See col. 9, lines 38-42.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teaching of Partain III by adding to the controlled-release formulation the compound of instant formula I, as motivated by Gaillard-Kelly (a) both references teach anti-alopecia compositions in topical formulations such as creams and lotions; and (b) Gaillard-Kelly teaches that the phenylimidazolidines are combined with other hair growth agents such as Minoxidil, which is also used in Partain invention. The skilled artisan would have had a reasonable expectation of successfully producing a stable, and enhanced anti-alopecia formula with constant, timed-release of the active ingredients, which protects the applied area of the skin.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, Gaillard-Kelly, and Encyclopedia of Controlled Drug Delivery as applied to claims 1, 2, 4, 7, 8, 11-13, 16, 17, 22, 23, 28, and 29 as above, and further in view of Lai (US 5916910).

The combined references fail to teach angiotensin converting enzyme inhibitors.

Lai teaches conjugates of dithiocarbamates with pharmacologically active agents, wherein dithiocarbamates are said to reduce cutaneous irritation and alopecia. See col. 3, lines 49-51. Captopril, fosinopril, felopdipine, nicardipine, and nifedipine are

taught as pharmaceutical agents that are added for modification. See col. 8, lines 51-54.

It would have been obvious to one of ordinary skill in the art at the time the present invention was made to have modified the teachings of the combined references by adding to the composition captopril as motivated by Lai because all the references are directed to treating alopecia, and Lai teaches that captopril are combined with other anti-alopecia agents. The skilled artisan would have had a reasonable expectation of successfully producing a composition that treats alopecia and hypertension.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, Gaillard-Kelly, and Encyclopedia of Controlled Drug Delivery as applied to claims 1, 2, 4, 7, 8, 11-13, 16, 17, 22, 23, 28, and 29 as above, and further in view of Ismail (US 5541220).

Partain, Gaillard, and Encyclopedia of Controlled Drug Delivery fail to teach methylxanthine compounds.

Ismail teach agents for the treatment protection of the skin. Exemplified is a capsule that can treat alopecia, which comprises pentoxifylin, vitamin E, and other ingredients.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add pentoxifylin to the composition of the composition of the combined references because Ismail and the references are directed to treating alopecia and Ismail teach pentoxifyiline as increasing blood circulation. The skilled artisan would have been motivated to add pentoxifyline to the composition of the

combined references because of the expectation of circulating the active agents of the composition though the body.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, Gaillard-Kelly, and Encyclopedia of Controlled Drug Delivery as applied to claims 1, 2, 4, 7, 8, 11-13, 16, 17, 22, 23, 28, and 29 as above, and further in view of Gaetani et al. (EP 0427625 A).

Gaillard-Kelly teaches to combine phenylimidazolidines with a product stimulating the growth of hair for the treatment of alopecia. See col. 9, lines 55 – 65. The reference fails to teach 2,4-diamino-6-butoxy-3-sulfopyrimidine hydroxide.

Gaetani teaches internal salts of 2,4-diamino-6-alkoxy-3-sulfoxypyridimine hydroxide for combating hair loss and inducing/stimulating hair growth. See abstract. Specifically disclosed is 2,4-diamino-6-butoxy-3-sulfoxypyridimidine hydroxide. See Example de composition 2 and 3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding 2,4-diamino-6-butoxy-3-sulfopyrimidine hydroxide to the composition, as motivated by Gaetani, because (a) the references are all directed toward combating hair loss; and (b) Gaillard-Kelly teaches to combine the phenylimidazolidines with hair growth stimulating agents to make an anti-alopecia composition. The skilled artisan would have been motivated to add 2,4-diamino-6-butoxy-3-sulfopyrimidine hydroxide to the composition of the combined references because of the expectation of further combating hair loss.

Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, Gaillard-Kelly, and Encyclopedia of Controlled Drug Delivery as applied to claims 1, 2, 4, 7, 8, 11-13, 16, 17, 22, 23, 28, and 29 as above, and further in view of applicants' own disclosure and Hocquaux et al. (WO 92/21317).

Gaillard-Kelly teaches to combine the phenylimidazolidines with a product stimulating the growth of hair for the treatment of alopecia. See col. 9, lines 55 – 65. The combined references fail to teach 2, 6-diamono-4-piperidinopyridine.

Hocquaux ('317) teaches compositions containing a pyridine-1-oxide for combating hair loss and inducing/stimulating hair growth. See '701,abstract. 2,6-diamino 4-peperdinopyridine 1-oxide is disclosed in Example 1. See instant claims 18 and 20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add the 2,6-diamino 4-peperdinopyridine 1-oxide to the composition of the combined references because (a) the references are all directed toward combating hair loss; and (b) Gaillard-Kelly teaches to combine the phenylimidazolidines with other hair growth stimulating agents to make an anti-alopecia composition. The skilled artisan would have been motivated to add 2,4-diamino-6-butoxy-3-sulfopyrimidine hydroxide to the composition of the combined references because of the expectation of successfully producing an enhanced composition for combating hair loss.

Claims 18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, Gaillard-Kelly, and Encyclopedia of Controlled Drug Delivery as

applied to claims 1, 2, 4, 7, 8, 11-13, 16, 17, 22, 23, 28, and 29 as above, and further in view of Hocquaux et al. (WO 91/19701).

Gaillard-Kelly teaches to combine phenylimidazolidines with a product stimulating the growth of hair for the treatment of alopecia. See col. 9, lines 55 – 65. The combined references fail to teach 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide.

Hocquaux ('701) teaches compositions containing 2, 6-diamino-1,3,5-triazine derivatives for combating hair loss and inducing/stimulating hair growth. See abstract. 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide is disclosed in Examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide to the composition of the combined references because Hocquaux ('701), because (a) the references are all directed toward combating hair loss; and (b) Gaillard-Kelly teaches to combine the phenylimidazolidines with hair growth stimulating agents to make an anti-alopecia composition. The skilled artisan would have been motivated to add the triazole compound of the Hocquaux ("701) to the composition of the combined references because of the expectation of successfully producing an enhanced composition for combating hair loss.

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Partain, Gaillard-Kelly, and Encyclopedia of Controlled Drug Delivery as applied to claims 1, 2, 4, 8, 11-13, 22, 23, 28, 29, 39, and 40 as above, and further in view of Cremophor RH 40 Technical Information (1997).

The combined references fail to teach polyoxyethylene hydrogenated castor oil.

Cremophor RH 40 Technical Information (Cremophor) teaches that POE hydrogenated castor oil is skin compatible and solubilizes hydrophobic pharmaceuticals including vitamin A (retinoic acid). See Solubilization. The reference teaches that the product forms clear solutions in water and ethanol with fatty acids and fatty alcohols. See Solubility.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding to the composition POE hydrogenated castor oil as motivated by Cremophor because (a) Gaillard, Partain, and Cremophor all teach using retinoic acid; and (b) Cremophor teaches that POE hydrogenated castor oil is a well known solubilizer in pharmaceutical/cosmetic art, which solubilizes hydrophobic pharmaceutical agents to form a clear solution. The skilled artisan would have had a reasonable expectation of successfully producing a stable, clear cosmetic composition comprising retinoic acid and the compound of instant formula (I).

Claims 1, 2, 4, 7, 10-13, 22, 23, 28, 29, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5658559) in view of Gaillard-Kelly and Encyclopedia of Controlled Drug Delivery.

Smith teaches a film-forming lotion composition which forms barrier on the surface of the skin to prevent evaporative loss of moisture from the skin, and protects the skin from environmental irritants. Polyvinylpyrrolidone/eicosene copolymers, polyvinylpyrrolidone/vinyl acetate copolymers, and polyvinylpyrrolidone/hexadecane copolymers are taught in col. 4, lines 14 – 32. See instant claim 10. The composition

also contains polysaccharide polymers which release the therapeutic agents in a time-controlled manner. See col. 4, lines 33 – 43. Also taught is polyquaternary polyvinylpyrrolidone such as polyquaternium-16 (polyvinylpyrrolidone/imidazolinium methochloride copolymers). See instant claims 39 and 40. The therapeutic agents include antiacne actives including benzoyl peroxide and vitamin A. See col. 5, lines 1-6. The composition of the invention comprises water and polyhydric alcohols such as propylene glycol and glycerine. See col. 8, lines 1 – 38. See instant claim 7.

Smith does not specifically mention that a plasticizer is used in the composition, but glycerine, as used in Example 14, is a well-known plasticizer in controlled release pharmaceutical art. See Encyclopedia of Controlled Drug Delivery, p. 307, Table 1; p. 309.

Smith fails to teach the compound of instant formula I.

Gaillard-Kelly, discussed above, teaches that the phenylimidazolidines of instant formula I is useful for treatment of acne, and further teaches to combine the active agent with retinol. See col. 9, lines 56 – 65. The formulations may be in the form of creams, pomades, and lotions. See col. 9, lines 29 – 36.

It would have been obvious to one of ordinary skill in the art at the time the present invention was made modify the teaching of Smith by adding to the occlusive, film-forming composition the phenylimidazolidine compound as motivated by Gaillard-Kelly, (a) both references are directed to acne treatment compositions with retinoid (Vitamin A); and (b) Smith teaches that the film-forming formulation provides controlled-release of the actives while protecting the skin and prevent loss of moisture of the skin;

and (c) Gaillard-Kelly teaches to combine the phenylimidazolidine compound with retinoid to make an anti-acne treatment composition. The skilled artisan would have had a reasonable expectation of successfully producing a stable and effective film-forming lotion which is useful for treating acne.

Response to Arguments

Applicant's arguments filed on September 26, 2006 have been fully considered but they are not persuasive.

Applicants' argue that there is no evidence to show that the use of a plasticizer in the Partain invention would have been obvious. Examiner reiterates that a particular type of a plasticizer, glycerine, is already practiced and illustrated by the reference. A reasonable skilled artisan would not have considered the illustration of using glycerine in an antihistamine lotion as an indication that the *only* application that glycerine is suitable is an antihistamine lotion. Rather, a reasonable artisan in pharmaceutical art would have considered the particular properties and functions of the ingredient, and used it to advance his formulations. This is not an impermissible hindsight but an objective view of what a skilled artisan would have done in view of prior arts available to him at the time of the present invention. Applicants' argument that there is no evidence in the record that glycerine is a desirable in a formulation is unfound, since Encyclopedia of Controlled Drug Delivery teaches to use plasticizer such as glycerine in a controlled'release formulations.

Applicants repeatedly assert that glycerine sometimes is not a plasticizer. In response, examiner does not need to rely on an inherency property of glycerine to make

the obviousness rejection here: the present rejection is not based on inherency that glycerine necessarily functions as a plasticizer, but that glycerine *is* a plasticizer according to the prior art.

The obviousness rejection made over Smith in view of Encyclopedia of Controlled Drug Delivery and Gaillard-Kelly is maintained for an analogous reason as explained above.

With respect to claim 14, applicants assert that it is the conjugated form of adriamycin and dithiocarbamate that reduces skin irritation and alopecia and not the dithiocarbamate itself. In response, examiner views that the rejection is still proper because the claimed limitation does not exclude such conjugated form of dithiocarbamate. Lai reference suggests that treatment for alopecia is needed for cancer patients, and a skilled artisan would certainly find the controlled release formulations for alopecia as taught by Partain/Encyclopedia/Gaillard-Kelly applicable in anticancer drugs.

Regarding the arguments on the remaining dependent claims, examiner maintains the position as discussed in the previous Office action dated December 14, 2006.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gina C. Yu whose telephone number is 571-272-8605. The examiner can normally be reached on Monday through Friday, from 8:00AM until 5:30 PM..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gina C. Yu
Patent Examiner

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER